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HPV Challenge Program

TEST PLAN

For

C3 Chlorinated Hydrocarbon Stream (CASRN 63890-96-5)

CASRN:	63890-96-5
Sponsor	The Dow Chemical Company Midland, Michigan
Date of Submission:	14 December 2004
Date of last Update:	10 December 2004

Test Plan for C3 Chlorinated Hydrocarbon Stream
(CASRN 63890-96-5)

I. SURROGATE JUSTIFICATION

CAS 63890-96-5 C3 Chlorinated Hydrocarbon Stream consists of several chlorinated 3-carbon chemicals which are produced as intermediate streams from several manufacturing product lines. Though somewhat variable, the largest volume components of CAS 63890-96-5 are 1,2-Dichloropropane (approximately 65%), Trichloropropene (8%), and 2-Chloropropene (6.5%) The remaining CAS 63890-96-5 C3 Chlorinated Hydrocarbon Stream is composed of a number of chlorinated propenes with no other single component present at more than a 5% of the total stream.

PDC will be used as a “surrogate” chemical for defining the toxicity of CAS 63890-96-5 C3 Chlorinated Hydrocarbon Stream as part of the HPV program based upon its high volume percent of the stream and the wealth of mammalian and environmental toxicity. PDC (65%), Trichloropropene (8%) and 2-Chloropropene (6.5%) all exhibit remarkably similar toxicity profiles (Bingham, 2001). While the acute oral and dermal LC₅₀'s of Trichloropropene and 2-Chloropropene are lower than those of PDC, toxicity via inhalation is very similar. The three components show very comparable subchronic NOAEL's, are all considered to be non-carcinogenic in *in vivo* testing, and all three have mixed or positive mutagenicity findings. They are similarly all considered to be non-teratogenic, although there were findings of mild delays in ossification in the fetuses at comparable dose levels. Based on the consistent toxicological profiles of the three compounds most abundant in the stream, it is reasonable to identify PDC as the surrogate for the stream.

Significantly, PDC has also been evaluated previously as part of the OECD SIDS program (<http://www.oecd.org>). It was judged to be “of low priority for further work” at SIAM 17 (November 2003) indicating the adequacy of its database for coverage of OECD SIDS endpoints. Information presented in the present HPV Test Plan and related IUCLID Robust Study Summaries were drawn heavily from the complimentary OECD SIDS documentation.

II IDENTITY

A. Identification of the Substance

CAS Number:	78-87-5
IUPAC Name:	1,2-Dichloropropane
Molecular Formula:	C ₃ H ₆ Cl ₂
Molecular Weight:	201.91
Synonyms:	PDC, Propylene Dichloride

The compound is a colorless liquid in the pure or neat state. Because of its structure, PDC has a high vapor pressure, and high partition coefficient (log K_{ow}). MacKay Level III fugacity modelling predicts that the substance will partition predominately to air.

B. Purity/Impurities/Additives

The compound is sold in its pure form.

C. Physico-Chemical properties**Table 1** Summary of physico-chemical properties

Property	Value
Physical state	colorless liquid
Melting point	-70 °C
Boiling point	95-96 ° C
Vapour pressure	66.2 hPa at 20° C
Water solubility	2800 mg/m ³ at 25° C
Partition coefficient n-octanol/water (log value)	2.0

III DEVELOPMENT OF ROBUST SUMMARIES AND STUDY SCORING CRITERIA

The Dow Chemical Company has chosen to use the IUCLID (International Uniform Chemical Information Database) format for preparation of robust summaries for the HPV program. Because many of the fields in the IUCLID database program are outside the scope of the HPV program, these fields are typically left blank in the IUCLID robust summary. Scoring of studies from company files or from the literature for reliability to fulfill the testing requirement for each endpoint used a system similar to that published by Klimisch *et al.* (1997). Studies were given a score of “1” if the data could be considered valid without restriction based on the completeness of the protocol and adequate details in reporting. Studies were given a score of “2” if the data and study design could be considered scientifically valid to address the endpoint but with restrictions due to lack of various technical or reporting details or deviations from current OECD guidelines. Studies were given a score of “3” if their conduct was not acceptable and “4” if there wasn’t enough information present to assign a reliability rating. However, a

study receiving a score of “4” could provide supplementary information that could be used to address the endpoint in a weight of evidence evaluation in the absence of other data.

IV TEST ENDPOINT RESULTS

Evaluation of the data for PDC leads to the conclusion that the quantity of data to adequately represent the toxicological and ecological profile of CAS 63890-96-5 C3 Chlorinated Hydrocarbon Stream. A summary of the data on each of the HPV/SIDS endpoints for the compound follows.

A. Physical Chemistry

Melting Point

IUCLID 2.1: PDC is a liquid in the neat or pure state with a melting point of -100.4°C (Mackay, 1993). The melting point is well-documented in peer-reviewed literature and databases. **No additional testing is required.**

Boiling Point

IUCLID 2.2: The boiling point for PDC is well-documented (Mackay, 1993). **No additional testing is required.**

Vapor Pressure

IUCLID 2.4: The vapor pressure for PDC has been well-documented in published literature and chemical handbooks. The experimental value is 66.2 hPa at 25°C (Mackay, 1993). **No additional testing is required.**

Partition Coefficient

IUCLID 2.5: Partition coefficient is well-documented (Mackay, 1993) for PDC. **No additional testing is required.**

Water Solubility

IUCLID 2.6.1: Measured data indicates that PDC is soluble in water. Measured aqueous solubilities of 2800 mg/m³ is reported. (Mackay, 1993) The low log K_{ow} also supports the reported data for water solubility. Sufficient data exist for this endpoint to characterize water solubility for the compounds. **No additional testing is required**

B. Environmental Fate**Photodegradation**

IUCLID 3.1.1: The compound does not absorb light >290 nm, and therefore direct photolysis is not possible (Howard, 1990). Vapour phase photolysis under simulated sunlight did not occur after prolonged exposure (period not stated). Experimental determination of its rate of reaction with hydroxyl radicals gave a half-life of >23 days. A computer estimate of its half-life due to H-atom abstraction by hydroxyl radical yields a calculated half-life of 7.12 days. **No additional testing is required**

Stability in Water (Hydrolysis)

IUCLID 3.1.2: PDC does not possess a molecular structure that contains functional groups subject to rapid hydrolysis under neutral ambient conditions; the ~~life~~ ^{half-life} at pH 7 is estimated to be 15. 8 years (Mackay, 1993).

Hydrolysis produces 1-Chlor-2-propanol and HCl. This testing endpoint is well characterized. **No additional testing is required.**

Environmental Transport

IUCLID 3.3.1: Based upon the EPIWIN Level III Fugacity Model, PDC is expected to stay primarily in air, as is shown in the following table. The assumption is for emissions to air only (according to U.S. EPA TRI Database, >99.9% of reported PDC emissions are to the atmosphere).

Predicted Environmental Partitioning of PDC

Compartment	Level I	Level III
Air	98.02	98.85
Water	1.82	0.93
Soil	0.16	0.21
Biota	<0.01	ND
Sediment	ND	<0.01

The EPIWIN Level I Fugacity Model results predict a similar fate. Advection in air accounts for 88.6%, and reaction in air for 11.2%, of the removal rate.

Advection and reaction in water, sediment, and soil account for 0.2% of removal rate. Although the values obtained using this model should not be regarded as quantitative, the model results are consistent with the properties of the compound.

No additional testing is required.

Biodegradation

IUCLID 3.5: Biodegradation is the conversion of a chemical by microorganisms in the environment into its simpler components and ultimately to carbon dioxide and its other constituent molecules. Chemicals are classified as readily biodegradable by the Organization for Economic Development (OECD) guidelines if there is a 70% degradation of dissolved organic carbon within a 10-day period during a typical 28-day laboratory protocol.

No biodegradation of PDC was detected when PDC (150 mg/l) was incubated aerobically with municipal activated sludge (1,000 mg/l mixed liquor suspended solids) for 28 days in an OECD 302B (modified EMPA Zahn-Wellens test), conducted according to GLP requirements (2002). However, there are published examples of acclimated municipal and other systems where PDC does undergo biodegradation, including addition of co-factors (acetate and methanol), and enrichment of cultures (Hauck and Hegemann, 1999; Hardy *et al.*, 1999). It is unknown if such conditions exist and if biodegradation occurs in the environment. A hydrolysis constant of 5.0×10^{-6} per hours (pH 7-9, 25° C) with a calculated half-life of 15.8 yr has been derived for water (MacKay *et al.*, 1993). These data indicate that there is sufficient information on the biodegradation potential of PDC. **No additional testing is required.**

C. Ecotoxicity

Toxicity to Fish

IUCLID 4.1: Consistent results were obtained from the fish toxicity studies of Walbridge *et al.* (1983) and Benoit *et al.* (1982) that demonstrate that PDC is of low acute toxicity towards freshwater fish (LC₅₀ ~140 mg/l). Although these studies pre-date current testing guidelines, they included analytical confirmation of achieved exposure concentrations which increases confidence in the reliability of the results obtained. In addition to the above, chronic aquatic toxicity data are available from a fish early life-stage (ELS). In the ELS test, a chronic NOEC of 6 mg/l was obtained for growth, and a chronic NOEC of 11 mg/l for survival, when *Pimephales promelas* was exposed to PDC for 28 days under flow-through conditions (Benoit *et al.*, 1982). The study included analytical verification of exposure concentration. **No additional testing is required.**

Aquatic Invertebrates

IUCLID 4.2: In a modern GLP-compliant guideline study using flow-through conditions and analytical confirmation of achieved concentration, Boeri (1988) obtained a 48 hr EC₅₀ of 55.9 mg/l for immobilization of *Daphnia magna*. The chronic invertebrate test, involving *Daphnia magna* (Boeri, 1988), was a GLP-compliant guideline investigation with analytical confirmation of exposure concentration. This returned a 21 day NOEC for effects on reproduction of 8.3 mg/l. Results from a 28 day study using the marine invertebrate *Mysidopsis bahia* (Ward *et al.*, 1989) gave a chronic NOEC of 4.1 mg/l for effects on mortality, reproduction and growth. The study was a GLP-compliant guideline investigation performed under flow-through conditions, with analytical

confirmation of achieved exposure concentration. **No additional testing is required.**

Aquatic Plants

IUCLID 4.3: Information on the acute toxicity of 1,2-dichloropropane on the salt-water algae *Skeletonema costatum* is available from Hughes (1988). This is a modern, GLP-compliant static guideline test, however GC analysis revealed variable losses of test substance from the screw-capped test vessels over the course of the study. As a result, no direct calculation of the EC₅₀ was possible. In recognition of this, Woodburn (2002a) used a time-weighted average AUC method (based on the measured dissipation rate of PDC from the test vessels) to calculate the no-effect concentration for this algal species. A NOEC_{120 hr} of 7.4 mg/l was thus obtained. In addition, Woodburn (2002b) calculated the percentage biomass inhibition and inhibition of growth rate over 72 hr based upon time-weighted average exposure concentration, and derived EC₅₀ values of 16.3 mg/l and 14.7 mg/l, respectively. De Groot (2002) also re-analyzed the original data from Hughes (1988) using linear interpolation after log transformation of the results obtained over the first 3 days of the study. This approach returned 72-hr EC₅₀ values of 15.1 and 15.8 mg/l for biomass and growth inhibition, respectively, and a 72-hr NOEC of 8.9 mg/l. Overall the data obtained by re-analysis of Hughes (1988) supports a 120-hr algal NOEC in the range 7.4-8.9 mg/l, with 72-hr EC₅₀ values of 15.1-16.3 mg/l for biomass inhibition and 14.7-15.8 mg/l for growth inhibition. **No additional testing is required.**

D. Toxicological Data

Acute Oral, Inhalation, and Dermal Toxicity

IUCLID 5.1.1-5.1.3 A number of studies are available which describe the acute toxicity of 1,2-dichloropropane in animals (summarized in the following table).

Although pre-dating modern guidelines and GLP, the results indicate that PDC is of relatively low inherent toxicity in animals after ingestion, skin contact, or inhalation. Given the high vapor pressure of 1,2-dichloropropane, inhalation exposure appears the most relevant route while rapid evaporation from skin would be expected to minimize any potential for local or systemic effects following dermal contact.

Summary of acute toxicity data for 1,2-dichloropropane

Endpoint	Species (details)	Result	Reference
Oral	Rat (Wistar)	2200 mg/kg bw	Smyth <i>et al.</i> , 1962; 1969
Inhalation LC ₅₀	Rat (4 hr)	2000 ppm 9.4 mg/l	Carpenter <i>et al.</i> , 1949; Smyth <i>et al.</i> , 1962
	Rat (7 hr)	> 2200 ppm > 10.3 mg/l	Highman and Heppel, 1946
	Guinea pig (7 hr)	> 2200 ppm > 10.3 mg/l	Highman and Heppel, 1946
Dermal LD ₅₀	Rabbit (occluded, 24 hr)	10,100 mg/kg bw	Smyth <i>et al.</i> , 1962; 1969

In contrast to the acute animal data, human case-reports suggest that the liver and red blood cells may be adversely affected following over-exposure by ingestion (Larcan *et al.*, 1977; Thorel *et al.*, 1986; Di Nucci *et al.*, 1988; Lucantoni *et al.*, 1992), inhalation (Pozzi *et al.*, 1985) or after prolonged, combined dermal and inhalative exposure (Fiaccadori *et al.*, 2003). Although quantitative exposure information is missing from many of these studies, and exposure to PDC is inferred rather than supported by analysis of the products involved, liver damage (hepatocellular necrosis, fibrosis, hypertension), increased serum transaminases,

haemolytic anaemia and intravascular coagulation were present reportedly in the subjects to varying extents. In two instances the subjects died after apparently ingesting 50-180 ml of industrial cleaning products (Larcan *et al.*, 1977; Di Nucci *et al.*, 1988) however the doses received by the remaining cases is not known. As a result of these findings, PDC is considered harmful by ingestion or inhalation.

No additional testing is required.

Irritation and Sensitization

IUCLID 5.2.1-5.3: Results from a GLP guideline skin irritation study (minimal redness and slight oedema), indicate that PDC is slightly irritating to skin (BASF, 1982). An early eye irritation study (BASF, 1965) reported marked redness, oedema and slight opacity 24 hr after instillation of 0.05 ml PDC into the conjunctival sac of a single rabbit. These effects were fully reversed after 8 days (no interim results available), and indicate that PDC is irritating to the eye.

Case reports provide equivocal evidence that PCD may cause allergic skin conditions after uncontrolled exposure in individuals with pre-existing dermatitis. In one study, 10 workers exposed to industrial preparations containing 10-40% PDC under conditions of poor occupational hygiene (hand cleaning using these products) exhibited an allergic response after patch testing with PDC with a threshold level of 2% (Baruffini *et al.*, 1989). However, all subjects suffered from pre-existing irritant skin-lesion and hand dermatitis that quickly resolved after cessation of exposure. In another brief report (Grzywa and Rudzki, 1981), two female workers with recurrent dermatitis responded to patch testing with 1% PDC as well as other substances present in the workplace. In contrast, results from an OECD 429 guideline mouse local lymph node assay (Woolhiser *et al.*, 2003) found no stimulation of lymphocyte proliferation in auricular lymph nodes

from mice treated with up to 80% PDC demonstrating that it was not a sensitiser under the conditions of this test. This lack of allergic potential in the mouse is consistent with structural considerations which provide no evidence of chemical alerts (reactive groups) that would indicate a potential to act as a sensitizer. In conclusion, based on the available data, PDC is considered to provide only equivocal evidence of an ability to cause skin allergy. **No additional testing is required.**

Repeated-Dose Toxicity

IUCLID 5.4: The oral repeat dose toxicity of PDC has been investigated extensively by NTP (1986) in a series of GLP-compliant studies using male and female F344 rats and B6C3F1 mice. Key aspects of the design of these studies, along with the main findings, are summarized in the following table. The results indicate that the liver is a target organ after gavage administration, with a chronic NOAEL of 125 mg/kg bw/day in female rats (males unaffected) and a chronic LOAEL of 125 mg/kg bw/day in male mice (females unaffected). Acanthosis of the stomach (indicative of persistent local irritation) was noted in mice (rats unaffected) with a chronic NOEL of 125 mg/kg bw/d in males and a chronic LOEL of 125 mg/kg bw/d in females. Body weight was decreased 14-24% in rats (chronic NOEL_{males} = 62 mg/kg bw/d, chronic NOEL_{females} = 125 mg/kg bw/d) whereas mice were unaffected (chronic NOEL = 250 mg/kg bw/d, both sexes). The overall NOAEL values following chronic administration of PDC were 62 and 125 m/kg bw/d for male and female rats respectively. No NOAEL was derived for mice of either sex, so the LOAEL was 125 m/kg bw/d.

The neurological consequences of repeated oral exposure to PDC have been investigated in F344 rats (n = 15/sex/group) given 0 (corn oil), 20, 65 or 200

mg/kg bw/day for 13 weeks by gavage (Johnson and Gorzinski, 1988). The study followed U.S. E.P.A. guidelines and was conducted to the standards of GLP. Prior to treatment, and at monthly intervals during the study, all animals were assessed for a number of endpoints including functional observational battery, hindlimb grip strength, and motor activity. After a 13-week treatment, 4 rats/sex/dose were randomly selected for terminal examination (including histopathological examination of brain, spinal cord and nerve) while the remainder were retained (no further treatment) for a 9 week recovery period. Transient clinical signs (lacrimation, blinking, decreased spontaneous motor activity) were reported on days 3-4 of treatment, and body weight was slightly decreased at week 13 in both sexes. There were no effects attributable to PDC in the functional observational battery, grip strength, or motor activity. Results from the gross and microscopic examination of the brain and nervous system revealed no treatment-related lesions. Overall, apart from a minor effect on body weight ($\text{NOAEL}_{\text{males}} = 20 \text{ mg/kg bw/day}$; $\text{NOAEL}_{\text{females}} = 65 \text{ mg/kg bw/day}$), no adverse structural or functional neurological consequences were apparent in rats following 13 weeks gavage administration of PDC at doses up to 200 mg/kg bw/day. The effects of repeated (13 week) inhalation exposure to PDC were investigated in rats, mice, and rabbits (Nitschke *et al.*, 1988). This GLP compliant study evaluated macroscopic and microscopic effects following exposures to 15, 50, and 150 ppm for rats and mice and 150, 500, and 1000 ppm in rabbits. Nasal respiratory changes, considered site-of-contact effects, were identified in rats, and slight reductions in body weight were also reported (NOEL of 15 ppm for both). No effects whatsoever were identified in mice (NOEL of 150 ppm). Results from rabbits demonstrated slight changes in red blood cell parameters, which were

indicative of a macrocytic normochromic, regenerative anemia (LOEL of 150 ppm for males; NOEL of 150 ppm for females).

Overall, results from repeat dose studies indicate that the liver is a target organ in rodents with a chronic oral NOAEL of 62-125 mg/kg bw/d in rats and a chronic LOAEL of 125 mg/kg bw/d in mice (no NOAEL established).

There were no adverse systemic effects in rats and mice following sub-chronic exposure to 150 ppm PDC (NOAEL), whereas red blood cell parameters (regenerative anemia) were altered in rabbits with a LOAEL of 150 ppm in males and a NOAEL of 150 ppm in females. Body weight was slightly but statistically significantly decreased in rats only (NOAEL 15 ppm) in these sub-chronic inhalation studies, with site-of-contact (irritative) changes present in stomach (mouse, NOAEL/LOAEL 125 mg/kg bw/d after oral gavage, dependent on sex) and nasal tissue (rat, NOAEL 15 ppm after inhalation). The toxicity profile has been well-studied and documented. **No additional testing required.**

1 **Summary of repeat oral toxicity data for 1,2-dichloropropane in rats and mice (gavage administration)**

Species	Treatment	NOAEL / LOAEL (mg/kg bw/day)	Comments
Rat	0, 125, 250, 500, 1000 or 2000 mg/kg bw/d for 2 wk (n = 5/sex/dose)	NOAEL = 500	All high-dose rats died during the study, with 15% decrease in bw at 1000 mg/kg bw/day (both sexes). Reddening of the renal medullae (1000 mg/kg bw/day) was the only other toxicologically-relevant effect.
	0, 60, 125, 250, 500 or 1000 mg/kg bw/d for 13 wk (n = 10/sex/dose)	NOAEL = 250	All high dose animals and 50% of males given 500 mg/kg bw/day died early. Body weight decreased 8-16% in 500 mg/kg bw/day groups. Centrilobular congestion, hepatic fatty change and centrilobular necrosis, affecting up to 50% of high dose animals, seen microscopically.
	Males: 0, 62 or 125 mg/kg bw/day for 103 wk Females: 0, 125 or 250 mg/kg bw/day for 103 wk (n = 50/sex/dose)	NOAEL _{males} = 62 NOAEL _{females} = 125	Survival of high dose females was significantly decreased relative to low dose and control groups (males unaffected). Body weight decreased 14-24% in high dose animals (both sexes). An increased incidence of hepatic foci of clear change and liver necrosis (high dose females only) were the only lesions of note.
Mouse	0, 125, 250, 500, 1000 or 2000 mg/kg bw/d for 2 wk (n = 5/sex/dose)	NOAEL _{males} = 250 LOAEL _{females} = 125	All high-dose mice died during the study, high levels of mortality also noted at 1000 mg/kg (both sexes) and 500 mg/kg (males only). No impact on body weight of survivors. Reddening of the renal medullae common in higher dose groups (both sexes), high incidence in males given 500 mg/kg, single occurrence in all lower female dose groups.
	0, 30, 60, 125, 250 or 500 mg/kg bw/d for 13 wk (n = 10/sex/dose)	NOAEL = 500	Minor (3-5%, not clearly dose-related) reduction in body weight, no histopathological lesions present.
	0, 125 or 250 mg/kg bw/day for 103 wk (n = 50/sex/dose)	LOAEL = 125	Survival of high dose females decreased relative to control (concurrent reproductive tract infection considered cause by NTP), survival of males unremarkable. Hepatocytomegaly and hepatic focal necrosis (low and high dose males), acanthosis of the stomach (high dose males, low and high dose females) and suppurative inflammation of the reproductive tract (all females, indicative of infection) were the only histopathological changes detected.

2 **Data from NTP (1986)**

Genetic Toxicity: Gene Mutations and Chromosome Aberrations

IUCLID 5.5 and 5.6: The mutagenic potential of 1,2-dichloropropane has been evaluated in a large number of microbial tests in bacteria and fungi, both in the absence and in the presence of exogenous metabolic activation (summarized by IARC, 1999). Overall, results from these tests are mixed with both positive and negative studies and are represented in the following table.

Summary of mutagenicity findings for 1,2-dichloropropane in *Salmonella typhimurium* tester strains (from IARC, 1999).

SALMONELLA TESTER STRAIN	Result		Dose* µg/ml	Reference
	Without S9	With S9		
TA100	+	+	5000	De Lorenzo <i>et al.</i> (1977)
	-	-	565	Stolzenberg and Hine (1980)
	+	+	2900	Principe <i>et al.</i> (1981) J Sci
	(+)	-	5000	Haworth <i>et al.</i> (1983)
TA1535	+	+	5000	De Lorenzo <i>et al.</i> (1977)
	+	+	2900	Principe <i>et al.</i> (1981)
	(+)	-	5000	Haworth <i>et al.</i> (1983)
TA1537	-	-	5800	Principe <i>et al.</i> (1981)
	-	-	1666	Haworth <i>et al.</i> (1983)
TA1538	-	-	5800	Principe <i>et al.</i> (1981)
TA98	-	-	5800	Principe <i>et al.</i> (1981)
	-	-	5000	Haworth <i>et al.</i> (1983)
TA1978	-	-	25000	De Lorenzo <i>et al.</i> (1977)

+ = positive result;

(+) = weakly positive (inconsistent response between independent repeats; <2-fold increase);

- = negative

* Either lowest effective dose (for positive study) or highest ineffective dose (for negative study)

However, in a GLP-compliant study with liquid pre-incubation conducted by the US National Toxicology Program, no mutagenic activity or cytotoxicity was detected when PDC (up to 2000 µg/plate) was incubated with four strains of *Salmonella typhimurium* (TA 98, TA 1537, TA 100, TA 1535) in the absence or presence of S9 fraction from Arochlor 1254-induced rats (NTP, 1986). A satisfactory response was obtained with the positive control substances, benzo(a)pyrene and MNNG. PDC was also not cytotoxic or mutagenic in these same tester strains when evaluated in the absence or presence of S9 using a plate incorporation methodology (up to 3150 µg/plate, in the absence or presence of glutathione supplementation; Oesch, 1979). Exposure to PDC vapor (atmosphere generated by evaporation of 0.3 - 10 ml of test

substance in a 20 l dessicator) also failed to produce a response in the organisms in the presence or absence of S9 and glutathione supplementation (Oesch, 1979), whereas dichloroethane (3 ml) was positive in TA100 and TA1535 under these same conditions.

Overall, PDC has returned consistently negative results in *Salmonella typhimurium* tester strains TA1537 and TA98 at up to 5800 µg/ml in the absence or presence of S9, whereas TA100 and TA1535 have returned inconsistent results under similar conditions.

When tested in mammalian cells *in vitro*, no mutation at the thymidine kinase locus was detected in L5178Y cells after incubation with up to 1000 nl/ml 1,2-dichloropropane in the absence of rat S9 (cytotoxic at >800 nl/ml), while assays in the presence of S9 provided evidence of mutagenicity at or around the threshold for cytotoxicity (80 nl/ml) (Myhr and Caspary, 1991). In an assessment of clastogenic potential, the number of chromosomal aberrations present in CHO cells exhibited a dose-related response (reported as a 5- or >16-fold increase) after incubation with 1370 or 1580 µg/ml PDC in the absence of S9, and an approximate 4-fold increase in the number of aberrant cells exposed to 660 or 950 µg/ml in the presence of S9 (NTP, 1986). In another series of *in vitro* experiments, CHO cells exhibited a dose-related increase in sister chromatid exchanges after exposure to PDC *in vitro*, with an approximate doubling in response after incubation with 376 or 1127 µg/ml PDC, both in the presence and absence of Arochlor 1254-induced rat S9 (NTP, 1986).

Results from a recent GLP compliant OECD 474 guideline mouse micronucleus study demonstrated no evidence of cytogenetic damage in bone marrow from CD-1 mice given up to 600 mg/kg bw by gavage (corn oil vehicle) on 2 consecutive days (Spencer *et al.*, 2003). Systemic toxicity (2° C drop in body temperature) was noted in high dose animals, while results from the range-finder investigation indicated that higher treatment levels (1000 mg/kg bw and above) were lethal. A satisfactory response was obtained with the positive control substance (cyclophosphamide). Based on toxicokinetic data demonstrating PDC is distributed evenly across all tissues, including bone, exposure of the bone marrow can be assumed for this study. The results demonstrate no potential for PDC to damage genetic material present in immature red blood cells.

Similarly, negative results were also reported from a modern, guideline rat dominant lethal assay (Hanley *et al.*, 1989) performed to GLP. Male SD rats (n = 30/group) received PDC in drinking water at doses equivalent to 0, 28, 91 or 162 mg/kg bw/day for at least 13 wk. The high dose was a saturated solution of PDC in water. They were then mated with untreated females for two successive one-week periods. A positive control group (cyclophosphamide, 100 mg/kg bw, 48 hr prior to mating) was included in the study. Mating and fertility indices were comparable between the control and PDC-treated groups (96-100%), but decreased significantly in the positive controls. Slight variations in number of corpora lutea, number of implantations, pre-implantation losses and resorptions rates were noted in the first or second week of mating in the low and high dose groups (mid-dose group not different from control), but the magnitude of the change was within the normal control ranges. In contrast, the positive control group showed a 2-fold increase in pre-implantation loss and a 10-fold increase in resorption rate. Overall it was concluded that PDC had no capacity to induce heritable mutations in male SD rats following at least 13-week oral treatment with up to 162 mg/kg bw/day.

Overall while findings from *in vitro* genotoxicity tests are inconsistent, including both positive and negative findings in bacterial and mammalian systems, results from recent GLP compliant guideline investigations demonstrate that PDC is not a somatic or germ cell genotoxicant *in vivo*, despite widespread distribution throughout the body. In addition, results from adequate carcinogenicity assays in rats and mice provide supplementary information on the mutagenic potential of 1,2-dichloropropane *in vivo*. The findings (limited to liver tumours in mice and no convincing evidence of carcinogenicity in the rat) indicate that the compound is not a genotoxic carcinogen. **No additional testing is required**

Carcinogenicity

IUCLID 5.7: The carcinogenic potential of PDC has been investigated in two long term oral gavage studies using F344 rats and B6C3F1 mice (NTP, 1986). Due to poor survival, statistical analysis of tumor incidence was adjusted for survival in both species.

No significant or treatment-related increase in tumor incidence was observed in male rats given 0, 62 or 125 mg/kg bw/day for 103 wk. Female rats given 125 or 250 mg/kg bw/day showed a positive trend for mammary adenocarcinoma incidence (adjusted rates: 3%, 5%, 27%), which was increased significantly in the high dose group. These were neither metastatic, anaplastic, nor highly invasive and were diagnosed by some NTP pathologists as highly cellular fibroadenomas (NTP, 1986). Affected high dose females showed a marked decrease in survival (32% alive at study end versus 74%-86% in the control and low dose groups) and a significant reduction (>20%) in body weight, suggesting that 250 mg/kg bw/day was in excess of the Maximum Tolerated Dose for PDC; compromised metabolic, immune, or hormonal status was possible under such conditions (NTP, 1986). It is pertinent that there was no increase in liver tumors despite the occurrence of chronic histopathological changes, including foci of clear change and necrosis. Based on these findings, NTP concluded that there was no evidence for the carcinogenicity of PDC in male rats, while in females given 250 mg/kg bw for 103 wk, there was equivocal evidence of an increased incidence of mammary adenocarcinoma; these were considered borderline malignant lesions by NTP, which occurred concurrently with decreased survival and reduced body weight gain. In mice, there was a positive trend for liver adenoma (adjusted for survival) in both sexes given 0, 125, or 250 mg/kg bw/day for 103 weeks. Tumor incidences in high dose males (45%) and both groups of treated females (17-19%) were increased significantly relative to the controls (20% in males, 3% in females). The findings in male mice occurred in the presence of hepatocytomegaly and hepatic focal necrosis in both treatment groups. The incidence of liver tumors in female mice was essentially identical in the two treated groups, despite a 2-fold difference in dose. High dose females also showed an increased incidence of thyroid tumors but this was not clearly dose-related (combined follicular cell carcinomas and adenomas, adjusted rates 3%, 0%, or 21% in control, low, and high dose groups), and occurred in the presence of liver changes (hepatocytomegaly, focal necrosis, tumors), which may have affected the metabolic and/or hormonal status of the animals. Body weights (both sexes) were unaffected by treatment, while survival at week 103 was reduced in treated females due to reproductive tract infection (70%, 58% and 52% for control, low and high dose animals; males unremarkable). NTP concluded that there was some evidence of carcinogenicity for PDC in male and female mice, based upon an increased

incidence of hepatocellular neoplasms, primarily adenomas (thyroid tumors disregarded). While the mechanism underlying these changes is unknown, the occurrence of histopathological liver lesions in male mice (LOAEL 125 mg/kg bw/day) suggests that chronic target organ toxicity may have played a contributing role in the expression of these benign tumors.

Hepatocellular adenoma is a common finding in control B6C3F1 mice. Historical control data for this lesion from contemporaneous NTP studies conducted to 1995 (corn oil, gavage, 16 studies) returned an incidence of 267/813 (33%) in males (range 14-58%) and 111/809 (14%) in females (range 2-28%) (Analytical Services Inc, 1995). Comparison of this historical control information with findings from the NTP study shows that the control incidence for males and females from this study (20%, 3%, respectively) was lower than the mean historical control data, while the incidence for high dose males (45%) and both treated females groups (17%, 19%) was below the upper bound of the historic control data. Spontaneous biological variation in the control data may therefore have influenced the results of this study. When reviewing the rat and mouse tumor findings reported by NTP, IARC (1999) concluded that 1,2-dichloropropane is not classifiable as to its carcinogenicity to humans (Group 3). Overall, these considerations indicate that PDC is not a direct-acting carcinogen, that there is equivocal evidence of an increase in mammary tumors in female rats, and that other factors (such as spontaneous biological variation) may have contributed to the increased incidence of mouse liver tumors.

No additional testing is required.

Reproductive Toxicity

IUCLID 5.8: The effect of PDC on the reproductive performance of male and female S-D rats was investigated in a GLP-compliant, guideline, 2-generation study by Kirk *et al.* (1990). PDC was administered in drinking water at levels of 0%, 0.024%, 0.1% or 0.24% (w/v), equivalent to received doses of 20-30, 70-130 or 130-250 mg/kg bw/day, respectively, for the parental generations; females received higher doses during lactation, equivalent to approx. 60, 200 and 450-500 mg/kg bw/day. Water consumption was decreased 20-50% in the mid- and high dose groups, possibly reflecting poor palatability linked to the presence of PDC. Gestational body weight gain was reduced by approximately 20% in high dose dams and 7-13% in mid dose females. Treatment-related hepatocellular granularity,

considered an adaptive change by the study pathologist, was present in males and females of both generations at all dose levels (incidence in high dose animals: $\leq 17\%$ in females; $<13\%$ for males). All other tissues, including reproductive organs from both sexes, were unremarkable. Despite the observed effects, reproductive function was unaffected in males and females of both generations. Although neonatal body weight was decreased, and neonatal mortality greater, in litters from high-dose dams consuming up to 250 mg/kg bw/d during pregnancy or up to 500 mg/kg bw/d during lactation, this appears secondary to maternal dehydration and a 20% reduction in gestational body weight gain, rather than a direct effect on reproduction. Live births, litter sizes and other pup parameters were unremarkable. Based on these findings, the study demonstrated a parental NOAEL of 20-30 mg/kg bw/day (0.024%; based upon body weight effects), a NOAEL in the offspring of 70-130 mg/kg bw/day (0.1%), and a reproductive NOAEL of 130-250 mg/kg bw/day (0.24%). Overall this study provides no evidence that PDC selectively targets the male or female reproductive system. **No additional testing is required**

Developmental Toxicity

IUCLID 5.9: The potential effects of PDC on embryonal/fetal development were investigated in two species by Kirk *et al.* (1995) in two GLP-compliant guideline studies. Pregnant S-D rats were treated with 0, 10, 30 or 125 mg/kg bw/day PDC in corn oil (gavage) on gestation days 6-15 inclusive and fetuses examined on GD 20, while pregnant New Zealand White rabbits received 0 (corn oil vehicle), 15, 50 or 150 mg/kg bw/day on GD 7-19, inclusive, followed by a fetal examination on GD 28.

Clear signs of maternal toxicity were present in high dose animals of both species. Rats given 125 mg/kg bw/day exhibited clinical signs (decreased movement and muscle tone, lacrimation, salivation) on GD 6 and 7, with an approx. 25% reduction in food and water consumption and a 30% reduction in body weight gain over the entire treatment period. Rabbits given 150 mg/kg bw/day showed a statistically significant net reduction in mean body weight gain on GD 7-20 (decreased 165 g) while controls showed a net gain (49 g) during the same period. Haematological changes were also noted in high dose rabbits (not evaluated in rats), with an approx. 20% reduction in red cell counts, haemoglobin concentration and haematocrit, while platelet and white cell counts were increased by 20-25%. Fetal examination revealed

a similarly low incidence of variations in control and treated groups of both species; the only treatment-related finding was a significant increase in delayed ossification of the bones of the skull in high dose rats and rabbits, indicative of a developmental delay. There was no evidence of any teratogenic effect. The NOAELs from this study are summarised in the following table.

Maternal and fetal NOAELs

	NOAEL (mg/kg bw/day)	
	Rat	Rabbit
Maternal toxicity	30	50
Fetal toxicity	30	50
Teratogenicity	125	150

Overall, results from these well-conducted developmental toxicity studies demonstrated the occurrence of mild fetotoxicity (delayed ossification) coincident with maternal toxicity. PDC was not teratogenic under the conditions of these investigations. **No additional testing is required**

V CONCLUSIONS

Evaluation of the existing data leads to the conclusions that a substantial quantity of data currently exist to adequately represent the toxicological and ecological screening profile of CAS 63890-96-5 C3 Chlorinated Hydrocarbon Stream, and these data support the conclusion that **no further testing is needed to satisfy endpoints for HPV/SIDS.**

V REFERENCES

BASF (1965) Study No XV 170, 3 September 1965. Report of BASF, Ludwigshaven, GER.

BASF (1982) Prüfung der akuten Hautreizwirkung/Atzwirkung gemmas OECD, study No. 81/358, 24 March 1982. Report of BASF, Ludwigshaven, GER.

Barruffini, A, Cirila, AM, Pisati, G, Ratti, R, and Zedda, S (1989). Allergic contact dermatitis from 1,2-dichloropropane. *Contact Dermatitis* **20**, 379-380.

Benoit, DA, Puglisi, FA and Olson, DL (1982). A Fathead minnow (*Pimephales promelas*) early life stage toxicity test method evaluation and exposure to four organic chemicals. *Environmental Pollution (Series A)* **28**, 189-197.

Bingham, E, Cohrssen, B, and Powell, C (2001). Patty's Toxicology, 5th Edition, pp. 222-228, J. Wiley and Sons, New York.

Boeri, RL (1988). Flow-through, chronic toxicity of 1,2-dichloropropane to the daphnid, *Daphnia magna*. Unpublished report, The Dow Chemical Company, Midland, MI.

De Groot, WA (2002). Unpublished communication, Solvay Pharmaceutical, Weesp, the Netherlands.

Di Nucci, Imbrani, M, Ghittori, S, Gregotti, C, Baldi, C, Locatelli, C, Manzo, L and Capodaglio, E. (1988). 1,2-Dichloropropane -induced liver toxicity: critical data and preliminary studies in rats. *Arch Toxicol Suppl.* **12**, 370-374.

Fiaccadori, E, Maggiore, U, Rotelli, C, Giacosa, R, Ardissino, D, De Palma, G and Mutti, A (2003). Acute renal and hepatic failure due to accidental percutaneous absorption of 1,2-dichloropropane contained in a commercial paint fixative. *Nephrol. Dial. Transplant.* **18**, 219-220.

Grzywa, Z and Ridzki, E (1981). Dermatitis from dichloropropane. *Contact Dermatitis* **7**, 151-152.

Hauck, R and Hegemann, W (1999). Investigations in microbial degradation of 1,2-dichloropropane in a fluidized bed reactor; Biol. Abwasserreinig. 12 (Behandlung von Abwaessern mit Halogen-Organischen Verbindungen), pp. 119-133)

Hanley, TR, Kirk, HD, Bond, DM, Firschau, HM and Johnson, KA (1989). Propylene dichloride: dominant lethal study in Sprague-Dawley rats. Unpublished report, The Dow Chemical Company, Midland, MI.

Hardy, L, Moeri, E and Salvador, M-C (1999). Rapid intrinsic degradation of chlorinated solvents at a manufacturing site in Brazil. Int. *In Situ* On-Site Biorem. Symp. 5th. Volume 1, pp. 19-28).

Howard, PH (1990). In: Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Vol II, p186. Lewis Publishers, Boca Raton, FL.

Hughes, J (1988). 1,2-Dichloropropane: the toxicity to *Skeletonema costatum*. Unpublished report, The Dow Chemical Company, Midland, MI.

IARC (1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 71, Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide (Part 3). IARC, Lyon, France, pp 1393-1400.

Johnson, KA and Gorzinski, SJ (1988). Neurotoxicologic examination of rats exposed to 1,2-dichloropropane (PDC) via gavage for 13 weeks. Unpublished report, The Dow Chemical Company, Midland, MI.

Kirk, HD, Hanley, TR, Bond, DM, Firchau, HM, Peck, CN, Stebbins, KE and Johnson, KA. (1990). Propylene dichloride: two generation reproduction study in Sprague-Dawley rats. Unpublished report, The Dow Chemical Company, Midland, MI.

Kirk, HD, Berdasco, NM, Breslin, WJ and Hanley, TR (1995). Developmental toxicity of 1,2-dichloropropane (PDC) in rats and rabbits following oral gavage. *Fund. Appl. Toxicol.* **28**, 18 - 26.

Klimisch, H.-J., Andreae, M. and Tillman, U. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol.* **25**, 1-5.

Larcen, A, Lambert, H, Laprevote, MC, Gustin, B. (1977). Acute poisoning induced by dichloropropane (abstract) *Acta Pharmacol. Toxicol.* **41**, 330.

Lucantoni, C, Grottoli, S and Gaetti, R (1992). Letter to the Editor *Toxicol. Appl. Pharmacol.* **117**, 113.

MacKay, D, Shiu, W Y and Ma, KC (1993). Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals, Vol III. Lewis Publishers, Boca Raton, FL.

Myhr, BC, Caspary, WJ (1991). *Environ. Mol. Mutagen.* **18**, 51 – 83.

Nitschke, KD, Johnson, KA, Wackerle, DL, Phillips, JE and Dittenber, DA (1988). Propylene dichloride: A 13 week inhalation toxicity study with rats, mice and rabbits. Unpublished report, The Dow Chemical Company, Midland, MI.

NTP (1986). Toxicology and carcinogenesis studies of 1,2-dichloropropane (propylene dichloride) (CAS No 78-87-5) in F344/N rats and B6C3F1 mice (gavage studies). NTP Technical Report Series No 263, NIH Publication No 86-2519.

Oesch, F (1979). Ames test for 1,2-dichloropropane. Report of BASF, Ludwigshaven, GER.

Pozzi, C, Marai, P, Ponti, R, Dell'Oro, C, Sala, C, Zedda, S and Locatelli, F. (1985). Toxicity in man due to stain removers containing 1,2-dichloropropane. *Br. J. Ind. Med.* **42**, 770-772.

Principe, P, Dogliotti, E, Bignami, M, Crebelli, R, Falcone, E, Fabrizi, M, Conti, G and Comba, P. (1981). Mutagenicity of chemicals of industry and agricultural relevance in *Salmonella*, *Streptomyces* and *Aspergillus*. *J. Sci. Fd. Agric.* **32**, 826-832.

Spencer, P Grundy, J., and Linscombe, V.A. (2003). Evaluation of 1,2-Dichloropropane in the Mouse Bone Marrow Micronucleus Test. Unpublished report, The Dow Chemical Company, Midland, MI.

Stolzenberg, SJ and Hine, CH (1980). Mutagenicity of 2- and 3-carbon halogenated compounds in the *Salmonella*/mammalian-microsome test. *Environ Mutagen* **2**, 59-66.

Thorel, JM, Bercoff, E, Massari, Ph, Droy, JM, Chassagne, Ph, Proust, B, Hemet, J and Bourreille, J. (1986). Toxicité du 1-2 dichloropropane A propose d'un cas avec hypertension portale. *Journal de Toxicologie Chimie et Experimentale* **6**, 247-252.

Timchalk, C, Bartels, MJ, Dryzga, MD and Smith, FA (1989). Propylene dichloride: pharmacokinetics and metabolism in Fischer 344 rats following oral and inhalation exposure. Unpublished report, The Dow Chemical Company, Midland, MI.

Walbridge, CT, Fiandt, JT, Phipps, GL and Holcombe, GW (1983). Acute toxicity of ten chlorinated aliphatic hydrocarbons to the Fathead minnow (*Pimephales promelas*). *Arch Environ Contam Toxicol* **12**, 661 - 666.

Ward, GS, Rabe, BA and Greer, DH (1989). 1,2-Dichloropropane: chronic toxicity to the mysid (*Mysidopsis bahia*) under flow-through conditions. Unpublished report, The Dow Chemical Company, Midland, MI.

Woodburn, K (2002a). Unpublished communication, The Dow Chemical Company, Midland, MI.

Woodburn, K (2002b). Unpublished communication, The Dow Chemical Company, Midland, MI.

Woolhiser, M and Anderson, P (2003). 1,2-dichloropropane (propylene dichloride): local lymph node assay in BALB/C mice. Unpublished report for The Dow Chemical Company, Midland, MI.

Summary of Endpoints and Data Quality

	PDC (78-87-5)	Adequacy	GLP?	Required Testing?
PHYSICAL CHEMISTRY				
Melting point, °C	-70°C	A_{calc}	No data	No
Boiling point, °C	95-96°C @ 1013hPa	A_{calc}	No data	No
Vapor Pressure @ 20°C	66.2 hPa	A_{calc}	No data	No
Water Solubility @ 25°C	2800 mg/m ³	A_{exp}	No data	No
Log K _{ow}	2.0	A_{calc}	No data	No
Density	1.155 g/cm ³ @ 20°C	A_{exp}	No data	No
ENVIRONMENTAL FATE				
Biodegradation	Not readily biodegradable	A_{exp}	Yes	No
Hydrolysis	½ Life at pH 7 ~ 15.8 years	A_{calc}	No data	No
Photodegradation	Does not absorb light at 290nm	A_{calc}	No data	No
Transport between Environmental Compartments: (Fugacity Level III Model) Default assumption: 1000 kg/hr released simultaneously into air, water, and soil.	98.85% to air 0.93% to water 0.21% to soil <0.01% to sediment	A_{calc}	No data	No
ECOTOXICITY				
Acute Toxicity to Fish (LC ₅₀)	LC ₅₀ (96h)=140 mg/L in <i>Pimephales promelas</i>	A_{exp}	No Data	No
Acute Toxicity to Aquatic Invertebrates (48hr EC ₅₀)	EC ₅₀ = 55.9 mg/L for immobilization of <i>Daphnia magna</i>	A_{exp}	Yes	No
	28-day NOEC = 4.1 mg/L in <i>Mysidopsis bahia</i>	A_{exp}	Yes	No
Toxicity to Aquatic Plants	In <i>Skeletonema costatum</i> : 72-hour EC ₅₀ = 14.7 - 15.8 mg/L NOEC _{120hour} = 7.4 - 8.9 mg/L	A_{exp}	Yes	No
TOXICOLOGICAL DATA				
Acute Toxicity (oral)	LD ₅₀ = 2200 mg/kg in Wistar rats	A_{exp}	No	No
Acute Toxicity (dermal)	LD ₅₀ > 10,100 mg/kg in rabbits	A_{exp}	No	No
Acute Toxicity (inhalation)	4-hour LC ₅₀ = 2000ppm	A_{exp}	No	No

	<i>(9.4mg/L) in rats</i>			
	<i>7-hour LC₅₀ > 2200ppm</i>	<i>A_{exp}</i>	<i>No</i>	
	<i>(10.3 mg/L) in rats</i>			
	<i>7-hour LC₅₀ > 2200ppm</i>	<i>A_{exp}</i>	<i>No</i>	
	<i>(10.3 mg/L) in Guinea pigs</i>			
Acute Skin Irritation	<i>In rabbits, a slight irritant</i>	<i>A_{exp}</i>	<i>Yes</i>	<i>No</i>
Acute Eye Irritation	<i>Redness, oedema, and slight opacity in rabbits, resolved at day 8.</i>	<i>A_{exp}</i>	<i>No</i>	<i>No</i>
Sensitization	<i>Negative in the LLNA / Positive in questionable human patch tests</i>	<i>A_{exp}</i>	<i>Yes / No</i>	<i>No</i>
Repeated Dose Toxicity	<i>Subchronic NOAEL = 250 mg/kg/day in rats</i>	<i>A_{exp}</i>	<i>Yes</i>	<i>No</i>
	<i>Chronic NOAEL = 62-125 mg/kg/day in rats</i>	<i>A_{exp}</i>	<i>Yes</i>	
	<i>Subchronic NOAEL = 250 mg/kg/day male mice, LOAEL = 125 mg/kg/day female mice</i>	<i>A_{exp}</i>	<i>Yes</i>	
	<i>Chronic LOAEL = 125 mg/kg/day in mice</i>	<i>A_{exp}</i>	<i>Yes</i>	
Genetic Toxicity-Mutation	<i>Results of tests are mixed. See text table.</i>	<i>A_{exp}</i>	<i>Yes / No</i>	<i>No</i>
Genetic Toxicity-Chromosomal Aberrations	<i>Results of tests are mixed. See text table.</i>	<i>A_{exp}</i>	<i>Yes / No</i>	<i>No</i>
Toxicity to Reproduction	<i>Reproductive function was unaffected in males and females of 2 generations; Parental NOAEL = 20-30 mg/kg/day; offspring NOAEL = 70-130 mg/kg/day; reproductive NOAEL = 130-250 mg/kg/day</i>	<i>A_{exp}</i>	<i>Yes</i>	<i>No</i>
Developmental Toxicity	<i>Mild fetotoxicity (delayed ossification) coincident with maternal toxicity in rats & rabbits. See text table for NOAEL's</i>	<i>A_{exp}</i>	<i>Yes</i>	<i>No</i>

TEST = Testing required to fill data gap

A = Adequate

NA = Not applicable due to physical / chemical properties

_{Calc} = Value determined by calculation or estimation

_{Exp} = Data derived via experimentation
